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### Metabolic interventions in heart failure

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# Chapter 1

## **Introduction**

## Introduction

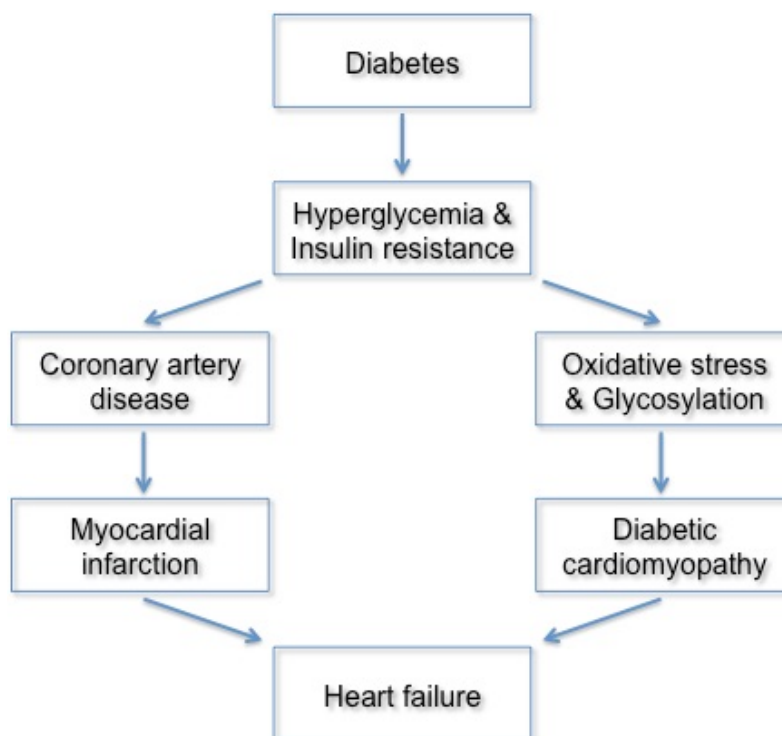
Heart failure (HF) is a major public health problem with a lifetime risk of almost 1 in 3 to develop this disease.<sup>1,2</sup> HF is the condition where the heart's blood supply does not suffice the body's demands. Despite improved treatment, the mortality rate for HF exceeds that of most malignancies.<sup>3</sup> As the most energy-consuming organ in the body, failing energy metabolism is thought to play an important role in the development of HF.<sup>4</sup> In this thesis, we investigated several aspects of metabolic interventions in HF. In the first part we investigated clinical aspects, including the position of  $\beta$ -blockers that have various metabolic effects. In this part we also describe the effect of coronary artery bypass grafting (CABG) in diabetic patients on HF development. In the second part we investigated the effects of A kinase interacting protein 1 (AKIP1) on cardiac remodelling and metabolism. This potential mitochondrial target for HF treatment was investigated using a transgenic mouse model.

### Metabolic interventions after revascularization

Several established therapies also affect cardiac metabolism. We focused on  $\beta$ -blockers, that are known to have several metabolic "side-effects", and it has been suggested that new onset diabetes and dyslipidaemia are possibly related to the use of  $\beta$ -blockers.<sup>5,6</sup> Nevertheless,  $\beta$ -blockers have been recommended as first line therapy for stable coronary artery disease (CAD) for over 5 decades, based on their potent anti-anginal effects and on extrapolation of the prognostic benefits that has been demonstrated after myocardial infarction (MI) and in patients with HF.<sup>7</sup> CAD is a leading cause of morbidity and mortality worldwide and is the main cause of systolic HF.<sup>8</sup> The lifetime risk of developing CAD is 30-50%.<sup>9</sup> While mortality rates are decreasing by continued refinements in the treatment of acute coronary syndromes, innovation in the treatment of stable CAD has been limited. The studies supporting the efficacy of  $\beta$ -blockers in patients with CAD predate the current era of urgent coronary revascularisation and were specifically designed to evaluate their effects on angina. Of note, there is no evidence that  $\beta$ -blockers provide superior angina relief compared to calcium channel antagonists, nitrates or ivabradine. Furthermore, the evidence for the efficacy of  $\beta$ -blockers after revascularization in patients with stable CAD is sparse.<sup>7</sup> Nevertheless,  $\beta$ -blockers are often continued in these patients, even when left ventricular function is preserved and there are no other indications for their continued use.<sup>10</sup> In **chapter 2** we therefore aimed to evaluate whether  $\beta$ -blocker therapy is associated with a reduced incidence of angina or cardiovascular events when continued after revascularization. For this purpose we performed a post-hoc analysis of the IMAGINE (Ischaemia Management with Acupril post bypass Graft via Inhibition of angiotensin coNverting Enzyme) trial database which comprised of low-risk patients with normal cardiac function, randomized to quinapril or placebo early

after elective coronary artery bypass grafting (CABG) surgery for CAD. This trial allowed us to study the low risk subgroup where we do not have evidence to support the routine use of  $\beta$ -blockers after CABG.

In **chapter 3**, we sought to determine whether CABG reduces the propensity to develop HF in diabetic patients with CAD and preserved cardiac function. Patients with diabetes have a two-fold higher lifetime risk to develop HF.<sup>11,12</sup> This is often linked to the propensity of diabetic patients to develop CAD and MI. Diabetic patients are also more prone to HF in the absence of CAD. The underlying mechanism is not completely clarified but is suggested to include increased oxidative stress and glycosylation leading to the activation of detrimental signal transduction pathways (Figure 1).<sup>13</sup> Diabetes is an important risk factor for CAD and the extent of CAD is more severe in diabetic patients. This results in a higher frequency of MI and contributes to the two-fold higher lifetime risk to develop HF in diabetic patients (Figure1). Accordingly, CAD is treated aggressively in diabetic patients and the threshold for choosing CABG surgery over PCI is reduced.<sup>14,15</sup> However, whether CABG also reduces the propensity to develop HF in diabetic patients is unknown.



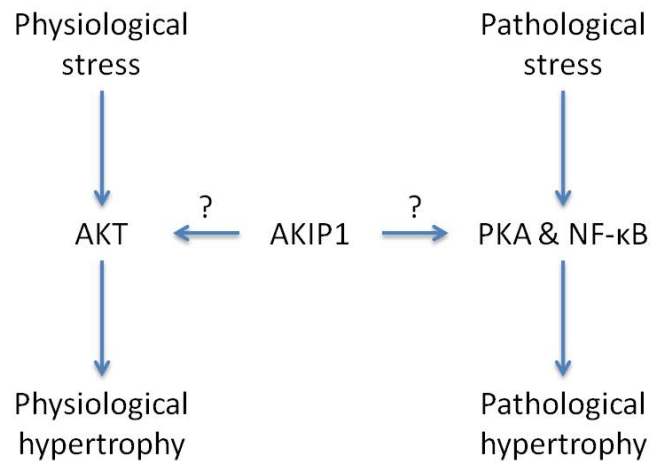
**Figure 1** Pathophysiological links between diabetes and heart failure, adjusted from Dei Cas et al.<sup>13</sup>

### **AKIP1 in cardiac stress**

Myocardial hypertrophy is the compensatory cardiac reaction to improve ventricular ejection performance after hemodynamic overload or injury. While initially myocardial hypertrophy reduces wall stress by restoring the ratio

between intracavitary pressure and wall thickness, it eventually decompensates and leads to HF.<sup>16,17</sup> This pathological hypertrophy is accompanied by a gene expression profile that resembles the embryonic heart.<sup>18</sup> Since it would be beneficial to only retain the adaptive aspects of physiological hypertrophy and prevent the deleterious collateral effects, we aim to determine what signaling pathways lead to hypertrophic decompensation. We previously performed genome wide transcription studies in a set of HF and hypertrophy models. We compared gene expression levels in 2 *in vivo* models (hypertension and post-MI) and 3 *in vitro* models in order to control for collateral differences in gene expression that are related to changes in hemodynamics rather than hypertrophic growth. One of the genes consistently upregulated was AKIP1.<sup>19</sup>

AKIP1 is a 21 kDa protein that was first identified as Breast Cancer Associated gene 3 (BCA3). In the initial studies, AKIP1 was found to be upregulated in several cancer cell lines, to tweak NF- $\kappa$ B and PKA activity,<sup>20,21</sup> and promote the induction of apoptosis.<sup>22,23</sup> In contrast, AKIP1 stimulates neovascularisation and tumor growth in other malignancies.<sup>24,25</sup> Therefore, AKIP1 may have different roles, depending on cell type and clinical condition. We previously performed several gain- and loss of function experiments of AKIP1 in cultured cardiomyocytes and found that AKIP1 promoted physiological growth in these cells.<sup>26</sup> AKT-activation served as a mediator of AKIP1-induced physiological hypertrophy. Furthermore, we found that AKIP1 stimulates mitochondrial respiration while reducing mitochondrial ROS productions, arguably making respiration more efficient.<sup>27</sup> In **chapter 4** we will review in more detail how different aspects of metabolic dysfunction, like decreased energy supply and exacerbation of oxidative stress, lead to deteriorating HF. Another group found that AKIP1 attenuates ischemia / reperfusion (I/R) injury in *ex vivo* perfused hearts.<sup>28</sup> Together, this suggests that AKIP1 has a vital role in both acute and chronic cardiac stress and that interventions targeting AKIP1 could offer a viable strategy to treat patients with heart disease. To investigate this hypothesis, we generated a transgenic mouse line with cardiomyocyte specific overexpression of AKIP1. In **chapter 5 & 6** we describe our studies exploring whether cardiac overexpression of AKIP1 translates into beneficial effects on both acute and chronic cardiac insults *in vivo* and whether it modulates physiological hypertrophy (Figure2).



**Figure 2** AKIP1 might influence cardiac hypertrophy development in response to different types of cardiac stress.

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Part 1

## **Metabolic interventions after revascularization**



